in the Overlap of Chronic Pelvic Pain Disorders. (Oral Presentation). The International Pelvic Pain Society 14th Annual Scientific Meeting on Chronic Pelvic Pain. Oct. 21, 2006. San Antonio, TX. *Award for Selected Presentation.

64. Ustinova, E.E., Fraser, M.O., Gutkin, D.W., Liang, R., and **Pezzone, M.A.** Neurogenic Sensitization of Bladder Afferents: The Role of Mast Cells and Neuropeptides. Basic Research in Interstitial Cystitis: Second Investigator's Meeting. October 25, 2006. Bethesda, MD.

65. Ustinova, E.E., Gutkin, D.W., Fraser, M.O., and **Pezzone, M.A.** Delayed Increase in Urinary Bladder Permeability Parallels Mast Cell Migration in TNBS Colitis. Digestive Disease Week. Washington, DC (May 2007).

66. Ustinova, E.E., Gutkin, D.W., Fraser, M.O., and **Pezzone, M.A.** Urinary Bladder Excitability Parallels Changes in Urothelial Permeability and Mast Cell Density in a Model of Neurogenic Cystitis. Annual Meeting of the Society of Neuroscience. San Diego, CA. November 6, 2007.

67. Ustinova, E.E., Gutkin, D.W., Fraser, M.O., and **Pezzone, M.A.** Neurogenic Cystitis Induced by Colonic Irritation Results in Increased Urothelial Permeability that Parallels Bladder Mastocytosis and Hyperactivity. American Urological Association Annual Meeting. Orlando, FL. **Podium Presentation.** (May 2008). J. Urology.

68. Ustinova, E.E., Gutkin, D.W., Fraser, M.O., and **Pezzone, M.A.** Mast Cells Play a Pivotal Role in the Development of Pelvic Organ Chronic Sensitization. Digestive Disease Week. San Diego, CA. **Oral Presentation.** (May 2008).

69. Ustinova, E.E., Bryant, A.P., Reza, T.L., Currie, M.G., and **Pezzone, M.A.** Oral Cyclic Guanosine Monophosphate (cGMP) Desensitizes Colonic Afferents in an Animal Model of Experimental Colitis. Annual Scientific Meeting of the American College of Gastroenterology. Orlando, FL. Oct 4, 2008.

70. Ustinova, E.E., Gutkin, D.W., Fraser, M.O., and **Pezzone, M.A.** Mast Cells Mediate Pelvic Organ Cross-Sensitization. Annual Meeting of the Society of Neuroscience. Washington, DC. November 16, 2008.

71. Ustinova, E.E., Gutkin, D.W., Fraser, M.O., and **Pezzone, M.A.** Pelvic afferents are Preferentially Sensitized to Chemical Stimuli During the Chronic Phase of TNBS Colitis: A Potential Role of Sensitized Mast Cells in the Maintenance of Chronic Visceral Pain. Digestive Disease Week. Chicago, IL. **Oral Presentation.** (June 2009).

72. Fitzgerald, J.J., and **Pezzone, M.A**. The Role of Mast Cells and PAR-2 Receptors in the Cross-Sensitization of Pelvic Afferent Nerves. Dean's Summer Research Program Symposium. October 6, 2009. Pittsburgh, PA.

73. Fitzgerald, J.J., Ustinova, E., **Pezzone, M.A.,** deGroat, W.C. The Role of Mast Cells and Protease Activated Receptor 2 in Pelvic Afferent Nerve Cross Sensitization. The Annual Meeting of the American Medical School Association. Washington, DC. (March 2011).

74. Fitzgerald, J.J., deGroat, W.C., Ustinova, E., and **Pezzone, M.A.** The Role Of Mast Cells And Protease Activated Receptors, Type-2 (Par-2R) in Pelvic Afferent Cross-Sensitization. The Annual Meeting of Experimental Biology. Washington, DC. (April 2011). FASEB J. March 17, 2011 25:1120.1

75. Fitzgerald, J.J., Pezzone, M.A., Ustinova, E., and de Groat, W.C. Release of mast cell mediators contributes to enhanced sensory mechanisms in the urinary bladder after TNBS colitis. Central Society for Clinical Research Annual Meeting. April 15, 2011. Chicago, Il.

76. Fitzgerald, J.J., deGroat, W.C., Ustinova, E., and **Pezzone, M.A.** Release of mast cell inflammatory mediators in the urinary bladder after colon irritation. American Urological Association Annual Meeting. Washington, DC. (May 2011). J. Urology.

77. Fitzgerald, J.J., Mupparapu, S.K., Pezzone, M.A., Ustinova, E., and de Groat, W.C. The role of PAR-2 and urothelium in bladder dysfunction after TNBS colon-bladder cross sensitization. Annual Meeting of the Society for Neuroscience. Washington, D.C. (November 2011).

78. Silos-Santiago, I., Hannig, G., Eutamene, H., Ustinova, E. E., Bernier, S. G., Ge, P., Jacobson, S., Jin, H., Reza, T., Shea, C., Kessler, M. M., Bryant, A. P., Kurtz, C. B., Bueno, L., **Pezzone, M. A.**, and Currie, M. G. Visceral Pain: Unraveling a novel endogenous pathway through uroguanylin/guanylate cyclase-C receptor/cGMP activation. 20th United European Gastroenterology Week. (October 2012). Amsterdam, The Netherlands.

PROFESSIONAL ACTIVITIES

TEACHING/STUDENT ADVISING:

- *Physical Diagnosis*, First year medical students, University of Pittsburgh School of Medicine (Four 60 min small group sessions/year) - 1998, 1999
- *Problem Based Learning in Gastroenterology*, Second year medical students. (4-6 90 min small group sessions/year) – 1997-2007 (Average score 4.6 out of 5)
- *Selective Course in Clinical Pharmacology, Peptic Ulcer Disease,* Fourth year medical students (One 90 min small group session/year) – 2001-02.
- *Diseases of the Colon, Digestion and Nutrition Course,* Second year medical students (1 hour lecture) – 2003
- *Drugs to Treat Gastric Acidity, Peptic Ulcer Disease, and Gastroesophageal Reflux Disease*, Second year medical students—2005-2010 (1 hr. lecture)
- *Drugs: Prokinetics and Antiemetics*, Second year medical students—2006-2010 (1 hr. lecture)

- *Physiology: Motility-Colon*, Second year medical students—2006-2008 (1 hr. lecture)
- *Colon Pathophysiology*, Second year medical students—2006-2008 (1 hr. lecture)
- Pharmacotherapy of Gastric Acidity, Peptic Ulcers, and GERD—Molecular Pharmacology 2081. Fall 2007-15. (1.5 hr. lecture) (Ongoing commitment)
- *F.A.S.T. (Faculty and Students Together) Advisor*—Faculty Advisor for 7 medical students. 2007-10
- *Physician Scientist Training Program Career Advisor*—Faculty Advisor for 3 students in the physician scientist track, 2007-10
- *Case Workshops in Gastroenterology*, 2nd year medical students (Four 80-min sessions with 9-18 students/group)-2008
- Clinical Preceptor in Gastroenterology & Hepatology, Duquesne University, Department of Physician Assistant Studies, 2013-present.
- Clinical Preceptor in Gastroenterology & Hepatology, Lake Erie College of Osteopathic Medicine 2014-present.

EDUCATION COMMITTEES:

- *Curriculum Design and Education Committee. Digestion and Nutrition Course, 2nd Year Medical Students, University of Pittsburgh--(June 2006-2009)*
- *Physician Scientist Training Program Steering Committee, University of Pittsburgh—(Jan 2007-2009)*
- *NIH/NIDDK Urology Strategic Planning Committee "Advancing Urologic Science and Career Development"—Worked directly with Robert Star and other thought leaders in Urology (Feb 2007)*
- *NIH/NIDDK Multidisciplinary Chronic Pelvic Pain (MAPP) Definition Working Group (2007-08) Chairperson: Evidence for an Interrelationship Between the Chronic Pelvic Pain Disorders—Dec 13, 2007*
- *NIH/NIDDK Defining the Urologic Chronic Pelvic Pain Syndromes: A New Beginning. An International Symposium. Expert Panel Member. June 16-17, 2008. Bethesda, MD.*

TRAINEES:

Pre-Medical Students:

Rhadika Patnam –Pre-med student Boston University. Summers of 2005-2007. Georgetown University for post-graduate studies. The

	Commonwealth Medical College, Scranton, PA. Residency in OB/GYN MUSC, Charleston, SC.
James Priestas	-Pre-med student University of Pittsburgh. Summer 2006-2008. Carnegie Mellon University's Health Administration Program. Health Strategy Manager at Accenture.
Tiffany DuMont, D.O.	-Pre-med student University of Pittsburgh. 2003-2004. Philadelphia College of Medicine. Pulmonary and Critical Care Fellow, Allegheny General Hospital, Pittsburgh, PA.
George Schatz	-Pre-med student Hiram College. Summer 2009. Undergraduate at Hiram College. Medical Student SUNY Stonybrook.

Medical Students:

Jocelyn Fitzgerald	-University of Pittsburgh Medical Student. Summer 2009, academic year 2009-10, Physician Scientist Training Program July 2010-June 2011. Ob-Gyn Resident, Johns Hopkins University.

Residents in Internal Medicine:

Santosh Mupparapu, M.D.	–Resident in Internal Medicine. Hospitalist, UPMC Passavant. Applying for Fellowship in Gastroenterology.
Suzanne Morrissey, M.D.	–Mentored during residency at the University of Pittsburgh Medical Center. Helped initiate a clinical study entitled, "Rectal Sensitivity in Patients with Interstitial Cystitis." Currently Faculty in Gastroenterology at Allegheny General Hospital, Pittsburgh, PA.
Daniel Chung, M.D.	–Mentored during residency with eventual acceptance into Gastroenterology fellowship at the University of Pittsburgh Medical Center. Currently a gastroenterologist in private practice in San Francisco, CA.
Surinder Devgun, M.D.	–Mentored as a post-internal medicine resident (motility fellow) at the University of Pittsburgh Medical Center. Trained in gastrointestinal motility and assisted in the development of a protocol for measuring motility in small bowel transplant patients. Several abstracts were published and an international oral presentation at small bowel transplant meeting was made. Advanced to Fellow in Gastroenterology at SUNY Health Center, Albany, NY. Currently in private practice in Rochester, NY.

Muhannad Kanbour, M.D. –Mentored for 1 year after completing foreign residency and assisted with the eventual acceptance into Internal Medicine residency at the University of Pittsburgh Medical Center. Assisted with a clinical study (multi-center) entitled, "Phase 3 Study to Determine the Efficacy and Safety of C1-Inhibitor (Human) Vapor Heated, IMMUNO, in subjects with Hereditary Angioedema (HAE)." Currently a hospitalist in Baltimore, MD.

Fellows in Gastroenterology:

Onki Cheung, M.D. –Mentored during fellowship (clinical motility). Abstract entitled, "Sensory Perception of Denervated Small Intestine Following Small Bowel Transplantation in Adults." Presented at Digestive Disease Week. Currently in private practice, Los Angeles, CA.

Post-Docs:

Ruomei Liang, M.D. –Former post-doc in lab. Part of NIH grant. Several projects and papers. Accepted into Family Practice Residency program at St. Margaret's Hospital. Currently in private practice in Northern California.

Elena Ustinova, Ph.D. –Former post-doc in lab. Part of NIH grant.

RESEARCH FUNDING:

ACTIVE—See Clinical Trials below.

PENDING--In vitro evaluation of the cytokine response to extracellular matric (ECM), determination of phenotype of immune cells from patients with ulcerative colitis (Stephen Badylak); paid consultant

INACTIVE—Basic Research Awards

1)	**MH 10157 (Pezzone)** NIMH National Research Service Award (NRSA)	1991-1994	100%
2)	GIDH Basic Research Award (Pezzone) (Glaxo Institute for Digestive Health)	1997-99 $35,000/yr.	50%
3)	**K08 DK02488 (Pezzone)** NIH/NIDDK Neuroimmune Mechanisms of Visceral Hyperalgesia	4/15/1999 – 1/31/2004 $116,200/yr.	75 %

The major goals of this project were to define the effects of acute and chronic colonic irritation on visceral afferent nerves specifically focusing on the role of mast cells and stress.

4) Samuel and Emma Winters Foundation (Pezzone) 1/1/2002 – 12/31/03 3%
$7,500.00

Constipation, Aging and Laxatives
The specific aims of this study include: determining the effects of aging on colonic histology and motility in young and aged Fisher-344 rats and determining if and how sub-chronic stimulant laxative administration affects colonic histology and motility in young and old-aged rats.

5) **R03 DK061380-01 (Pezzone) (PI)** 1/1/2004-12/31/06 5%
NIH/NIDDK $50,000/yr.
Neuroimmune Mechanisms of Visceral Pain

This award is linked to K08 DK02488. Studies here will accentuate those in the K08 award and will also involve in a preliminary fashion the investigation of colon afferent nerve changes following acute and chronic urinary bladder irritation.

6) **R01 DK066658-01 (Pezzone) (PI)** 9/1/2003 – 8/31/2009 55 %
NIH/NIDDK $211,500/yr.
Neurogenic Pathogenesis of Interstitial Cystitis

The major goals of this project are to determine how colonic irritation can lead to changes in lower urinary tract motor and sensory function. A neurogenic model of interstitial cystitis will be studied. These studies will evaluate the overlap of chronic pelvic pain disorders.

7) **R01 NS050758-01 (Davis, B.) (Co-investigator)** 12/1/2004- 11/30/2008 5%
NIH/NINDS $13,038/yr.
Characterization and Plasticity of Visceral Nociceptors

The major goals of this project are to determine how colonic irritation in neonatal rats can lead to visceral hypersensitivity at maturity.

8) Microbia MDP-100-008, CSA-2694 (Pezzone) (PI) 11/1/07- 09 3%
Microbia, Inc. $15,085

Effect of MM-416775 on the Sensitivity of Pelvic Visceral Afferents

9) Effect of MM-431343 (Pezzone) (PI) 12/08-09 3%
Ironwood Pharmaceuticals, Inc. (Formerly Microbia) $12,368

Effect of MM-431343 on the Sensitivity of Pelvic Visceral Afferents

10) Effect of Lubiprostone (Pezzone) (PI) 12/08-present 3%
Takeda Pharmaceuticals North America, Inc. $36,690

Effect of Lubiprostone on Pelvic Visceral Afferents

11) Effect of NS4591 (Pezzone) (PI) NeuroSearch A/S (Denmark)	12/08-present $14,992.98	3%

Effect of NS4591 on Acute and Sub-acute Bladder Afferent Sensitization

ACTIVE—Clinical Trials

1) A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group Trial of Linaclotide (72 ug or 145 ug) Administered Orally for 12 Weeks to Patients with Chronic Idiopathic Constipation (Ironwood Pharmaceuticals, Inc.)

2) In vitro evaluation of the cytokine response to extracellular matrix (ECM) and determination of the phenotype of immune cells in fixed specimens from patients with ulcerative colitis

INACTIVE—Clinical Trials

1) Randomized, Double Blind, Placebo-Controlled, Multicenter Study of a Subcutaneous Formulation of Icatibant for the Treatment of Hereditary Angioedema (Amendment 2 – Modified Open-Label Extension Phase) (Jerini)

2) MCP-103-202: A Randomized, Multicenter, Double-blind, Placebo-controlled, Dose-range-finding, Parallel-design, Phase 2 Trial of Oral Linaclotide Acetate Administered to Patients with Irritable Bowel Syndrome with Constipation (Microbia)

3) MCP-103-201: A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Dose-Range-Finding, Parallel-Group, Phase 2 Trial of Oral Linaclotide Acetate Administered to Patients with Chronic Constipation (Microbia).

4) Protocol SPI/0211OBD-0631: A Multicenter, Randomized, Placebo-controlled, Double-blinded Study of the Efficacy and Safety of Lubiprostone in Patients with Opioid-induced Bowel Dysfunction (Sucampo)

5) Protocol SPI/0211OBD-06S1: A Multicenter, Open-labeled Study of the Long-term Safety and Efficacy of Lubiprostone in Patients with Opioid-induced Bowel Dysfunction (OBD) (Sucampo)

6) A Randomized, Double-blind, Placebo-controlled Study of AGI-003 (Arverapamil) in the Treatment of Irritable Bowel Syndrome with Diarrhea (IBS-D) (AGI Therapeutics)

7) A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group Trial of Linaclotide Administered Orally for 12 Weeks Followed by a 4-Week Randomized Withdrawal Period in Patients with Chronic Constipation. MCP-103-303 (Ironwood Pharmaceuticals, Inc.)

8) An Open-label, Roll-over Safety Study of AGI-003 (Arverapamil) in the Treatment of Irritable Bowel Syndrome with Diarrhea (IBS-D). Clin-AGI003-007 (AGI Therapeutics).

9) An Open-label, Long-term Safety Study of Oral Linaclotide Administered to Patients with Chronic Constipation or Irritable Bowel Syndrome with Constipation. MCP-103-305. (Ironwood Pharmaceuticals, Inc.)

10) A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group Trial of Linaclotide Administered Orally for 26 Weeks in Patients with Irritable Bowel Syndrome with Constipation. MCP-103-302 (Ironwood Pharmaceuticals, Inc.)

11) A Randomized, Double-blind, Placebo-controlled, Parallel group, Dose ranging, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-27018966 in the Treatment of Patients with Irritable Bowel Syndrome with Diarrhea (Furiex Pharmaceuticals Protocol 27018966IBS2001)

ADVISORY BOARDS:

- *Glaxo Managed Care Advisory Board for IBS (6/00, Toronto)*
- *Novartis Regional Advisory Board on IBS (8/00, Las Vegas)*
- *Glaxo Functional Dyspepsia Advisory Board (10/00, New York)*
- *Sucampo Regional Advisory Board on Constipation (11/07, Philadelphia)*
- *Frontiers in Urology Advisory Board Meeting (7/08, San Francisco)*

GRANTS REFERREED/STUDY SECTION:

- *Katholieke Universiteit Leuven—2003*
- *ZRG1-UKGD 01 B, NIH. March 15, 2004*
- *ZRG1 RUS-D 12, NIH. March 16, 2004*
- *ZRG1 CFS-E(50)R, NIH.* Neuroimmune Mechanisms and Chronic Fatigue Syndrome. January 26, 2006.

ABSTRACT REVIEWER:

- *American Gastroenterological Association 2006 Annual Meeting--Digestive Disease Week Immune Modulation of Motility*
- *Science2006. University of Pittsburgh (October 2006).*
- *American Gastroenterological Association 2007 Annual Meeting--Digestive Disease Week Motility & Nerve-Gut Interactions—Section Chair*

NATIONAL MEETING SESSION CHAIR:

- *American Gastroenterological Association 2006 Annual Meeting--Digestive Disease Week Ion Channels and Receptors on Gastrointestinal Afferents (May 13, 2006) Los Angeles, CA*
- *Basic Research in Interstitial Cystitis: Second Investigators' Meeting (October 25, 2006)—*

Bladder Pain and Neurophysiology

PLANNING COMMITTEE:

- *Basic Research in Interstitial Cystitis: Second Investigators' Meeting (October 25, 2006)*
- *American Motility Society: Diabetes and the Gut. (March 1-4, 2007)*

JOURNALS REFEREED:

- *American Journal of Physiology*
- *Brain, Behavior, & Immunity*
- *Brain Research*
- *Gastroenterology*
- *Journal of Anatomy*
- *Journal of Neuroscience*
- *Journal of Spinal Cord Medicine*
- *Pain*
- *Urology*
- *World Journal of Gastroenterology*

JOURNAL EDITORIAL BOARDS:

- *World Journal of Gastroenterology*

INVITED LECTURESHIPS/PRESENTATIONS:

The University of Pittsburgh and Carnegie Mellon University M.D./Ph.D. Program Annual Summer Retreat. (1996) Boyce Park, Monroeville, PA.

Department of Medicine, University of Pittsburgh School of Medicine, "Stress, Immune Regulation, and Disease." (1997). Pittsburgh, PA.

GI Grand Rounds, UPMC. Gastric Stump Carcinoma, January 28, 1998, Pittsburgh, PA.

GI Grand Rounds, UPMC. Diffuse Esophageal Spasm, March 11, 1998, Pittsburgh, PA.

GI Grand Rounds, UPMC. ACE Inhibitor-induced Visceral Angioedema, April 15, 1998. Pittsburgh, PA.

GI Grand Rounds, UPMC. Superior Mesenteric Artery Syndrome, May 6, 1998, Pittsburgh, PA.

GI Grand Rounds, UPMC. Campylobacter Diarrhea and GBS. June 24, 1998.

GI Grand Rounds, UPMC. Celiac Sprue, October 7, 1998, Pittsburgh, PA.

GI Grand Rounds, UPMC. Visceral Hyperalgesia, April 7, 1999.

GI Grand Rounds, UPMC. Secondary Biliary Cirrhosis, May 14, 1999.

GI Grand Rounds, UPMC. Acute Porphyria, September 29, 1999.

Intracity Grand Rounds. Gut Club. November 8, 1999.

IBS Awareness. December 1999, Erie, PA.

GI Grand Rounds, UPMC. H. pylori and Gastric MALT Lymphoma, February 16, 2000, Pittsburgh, PA.

West Virginia Gastrointestinal Conference on IBS, April 2000, Snowshoe, WV.

IBS Update: Greenbrier Valley Medical Society, May 9, 2000, White Sulphur Springs, WV.

Medical Grand Rounds, Citizens General Hospital. IBS, May 2, 2000, McKeesport, PA.

GI Grand Rounds, UPMC. Collagenous and Microscopic Colitis, June 7, 2000, Pittsburgh, PA.

The Gastroenterologist as a Bench Scientist. Nemacolin Woodlands. Nov 9, 2002. Farmingham, PA.

Vulvodynia—Toward Understanding a Pain Syndrome. National Institutes of Health. Bethesda, MD. April 14, 2003. Neurophysiology of the Pelvis.

Neurogenic Cross-Sensitization of Pelvic Viscera: Implications for Interstitial Cystitis and Irritable Bowel Syndrome. University of Oklahoma Health Sciences Center. Department of Physiology. Oklahoma City, OK. May 28, 2003.

Neural Cross-Talk and Cross-Sensitization in the Pelvis. Post-DDW Review: Gastroenterology and Hepatology Advancements from Digestive Disease Week. Renaissance Pittsburgh Hotel, Pittsburgh, PA. June 6, 2003.

Neurogenic Cross-Sensitization of Pelvic Viscera: Implications for Interstitial Cystitis and Irritable Bowel Syndrome. September 18, 2003. Pittsburgh, PA. Monthly seminar of the M.D./Ph.D. program.

Neurogenic Cross-Sensitization of Pelvic Viscera: Implications for Interstitial Cystitis and Irritable Bowel Syndrome. University of Texas Medical Branch. Division of Gastroenterology. Galveston, TX. October 24, 2003.

GI Grand Rounds. University of Alabama at Birmingham. Birmingham, AB. November 6th, 2003.

GI Grand Rounds. University of Chicago. Chicago, IL. November 14th, 2003.

GI Grand Rounds. Columbia University. New York, NY. November 24th, 2003.

Pharmacologic Approaches to IBS. Gastroenterology and Motility Conference. Renaissance Pittsburgh Hotel, Pittsburgh, PA. December 6th, 2003.

University of Pittsburgh Pain Research Conference. Neurogenic Cross-Sensitization of Pelvic Viscera: Implications for the Overlap of Irritable Bowel Syndrome, Interstitial Cystitis, and Chronic Pelvic Pain March 31, 2004.

GI Grand Rounds. Duke University, Durham, NC. April 22, 2004.

24th Annual Scientific Meeting of the American Pain Society. Visceral Pain Processing: Mindblowing New Perspectives. Boston, MA. April 1, 2004.

New Advances in Diagnosis & Treatment of Immune-Mediated Diseases. Immunology of Crohn's Disease and New Treatment Modalities. October 27, 2007. Pittsburgh, PA.

Society for Urodynamics & Female Urology 2008 Winter Meeting. Pelvic Organ Neurophysiology: Implications for Chronic Pelvic Pain and the Overlap of Chronic Pelvic Pain Disorders. February 29, 2008. Miami, FL. http://webcasts.prous.com/SUFU2008/

Frontiers in Urology. Peripheral and Central Processing of Bladder Afferent Nerve Activity. Cross-Talk and Sensitization of Bladder Afferent Nerves. July 25, 2008. San Francisco, CA.

GI Grand Rounds. University of North Carolina Center for Functional GI and Motility Disorders. Pelvic Afferent Cross-sensitization and the Overlap of Chronic Pelvic Pain Disorders. Chapel Hill, NC. December 19, 2008.

2009 Pelvic Health Patient Education Day. PURE HOPE 4th Annual Women's Pelvic Health Conference Keynote Speaker. Irritable Bowel Syndrome & Overlapping Chronic Pelvic Pain Disorders. January 24, 2009. Houston, TX. (Baylor University).

8th International Symposium on Functional Gastrointestinal Disorders. Mini Symposium: Overlap of GI with Somatic Syndromes. Interstitial Cystitis. April 19, 2009. Milwaukee, WI.

GI Grand Rounds. Columbia University. New York, NY. Irritable Bowel Syndrome and Overlapping Chronic Pelvic Pain Disorders. June 15th, 2009.

Update in Internal Medicine. Evidence-Based Approaches to Common Medical Problems. Constipation: Evaluation and Management. October 29, 2009. Pittsburgh, PA.

Noontime Lecture The Washington Hospital Family Practice Residency. Constipation: Evaluation and Management. December 18, 2009.

Noontime Lecture The Washington Hospital Family Practice Residency. Drugs to Treat Gastric Acidity,

Peptic Ulcer Disease, and Gastroesophageal reflux disease. January 15, 2010.

Grand Rounds. Washington Hospital, Washington, PA. New Treatments for Irritable Bowel Syndrome and the Role of the Small Bowel. December 1, 2010.

Colon Cancer Screening 2011. Washington Hospital, Washington, PA. March 31, 2011.

GI Grand Rounds. University of Arkansas, Little Rock. Irritable Bowel Syndrome and Overlapping Chronic Pelvic Pain Disorders. June 1st, 2011.

Centers for Rehab Services--Women's Rehab and Men's Health Grand Rounds. University of Pittsburgh. Evaluation and Management of Constipation and Pelvic Pain. July 26th, 2011.

Indiana Dental Hygienists' Association's 66th Annual Professional Development Day. Key note speaker. Celiac Disease: Systemic and Oral Manifestations, Diagnosis, and Nutritional Management. Indianapolis, IN. November 3rd, 2012.

Internal Medicine Grand Rounds. Georgia Regents University. Pelvic Pain and the Overlap of Chronic Pelvic Pain Disorders. March 5, 2013. Augusta, Georgia.

The Washington Hospital Annual Scientific Day. Geriatrics: The Boomers Cometh. Constipation, Evaluation, and Management. May 3, 2013.

Erie Gut Club. Erie, PA. Irritable Bowel Syndrome and Overlapping Chronic Pelvic Pain Disorders. October 23, 2013.

Annual Meeting of the American Urological Association. State-of-the-Art Lecture. Role of Gastrointestinal Tract in Urologic Disease. May 19, 2014. Orlando, FL.

MEDICAL-LEGAL CONSULTING:

- *Fancher v. Curon* (August-December 2004)
  Deposition 12/17/04 in support of defense
  U.S. District Court, Western District of KY, Louisville Division

- *Hal Young v. GNC* (2006)
  Expert Witness

- *Berkey v. Locust Grove Facility Operations (2012)*
  Medical Consultant

- *Marks v. Feng (2013)*
  Medical Consultant

- *Mangone v. Morris County Surgery Center (2014)*
  Medical Consultant

- *Goodwin v. University Hospitals Richmond Medical Center (2014)*
  Medical Consultant

LIST of CURRENT RESEARCH INTERESTS:

- Visceral afferents in the gastrointestinal and urinary tracts and their role in visceral hyperalgesia
- Pelvic floor dysfunction and combined colonic and bladder hyperalgesia
- Chronic pelvic pain and the overlap of chronic pelvic pain disorders
- Role of ECM (extracellular matrix) in the management of ulcerative colitis
- Brain-gut-immune interactions in gastrointestinal disorders
- Stress effects on the brain-gut axis and inflammatory bowel disorders
-

SERVICE:

- Medical school admissions interviewer--2002-2003, 2006-2007

COMMUNITY:

• 2013-14	Manager	Steel City Predators 18U	Club Baseball Team
• 2012-13	Assistant Manager	Steel City Predators 17U	Club Baseball Team
• 2011-12	Assistant Manager	Steel City Predators 16U	Club Baseball Team
• 2010-11	Assistant Manager	Steel City Predators 14U,19U	Club Baseball Teams
• 2009-10	Assistant Manager	Steel City Predators 18U	Club Baseball Team
• 2008-09	Assistant Manager	Steel City Predators 17U	Club Baseball Team
• 2007-08	Assistant Manager	Pittsburgh Elite 16U	Club Baseball Team
• 2006-07	Assistant Manager	Pittsburgh Elite 15U	Club Baseball Team
• 2005-06	Assistant Manager	Pittsburgh Wild Things 14U	Club Baseball Team
• 2004-05	Assistant Manager	Pittsburgh Wild Things 13U	Club Baseball Team
• 2003-04	Manager	Pittsburgh Wild Things 12U	Club Baseball Team
• 2003	Manager	Upper St. Clair 11-12's	Rec Baseball Team
• 2002	Manager	Bethel Church League 9-10's	Rec Baseball Team
• 2001	Manager	Scott Athletic Assoc. 5-6's	Rec Baseball Team

- Camp Physician—Deer Valley, PA. 2004, 2006, 2008, 2010—yearly 3 day, school-sponsored ecology field trip for 6th graders at Boyce Middle School, Upper St. Clair, PA.
- Physician Volunteer—Birmingham Clinic for Homeless—May 2011 to present.
- Physician Volunteer—Dominican Republic Outreach Program—Nov 2011.

Exhibit B

To the Expert Report of

Dr. Michael A. Pezzone, M.D., Ph.D.

Additional Materials Considered

Publications.

Barnett, R. The demonstration with the electron microscope of the end products of histochemical reactions in relation to the fine structure of cells. Exptl. Cell Res. 1959;7:65.

Dannaeus, A., Inganas, M., Johansson, S.G.O., and Foucard, T. Intestinal uptake of ovalbumin in malabsorption and food allergy in relation to serum IgG antibody and orally administered sodium cromoglycate. Clinical Allergy 1979; 9:263-70.

Heyman, M., Boudraa, G., Sarrut, S., Giraud, M., Evans, L., Touhami, M., Desjeux, J.F. Macromolecular transport in jejunal mucosa of children with severe malnutrition: a quantitative study. J Pediatr Gastroenterol Nut 1984; 3:357-363.

Husby, S. Normal immune responses to ingested foods. Journal of Pediatric Gastroenterology and Nutrition 2000; 30:s13-19.

Husby S, Jensenius JC, Svehag SE. Passage of undegraded dietary antigen into the blood of healthy adults. Scand J Immunol 1985c;22:83–92.

Husby, S., Jensenius, S.C., Svehag, S.E. Passage of undegraded dietary antigen in the blood of healthy adults. Further characterization of the kinetics of uptake and the size of distribution of the antigen. Scan J Immunol 1986; 24:447-455.

Jakobsson, I., Lindberg, T., Lothe, L., Axelson, I., Benediktsson, B. Human B-lactoglobulin as a marker of molecular absorption. Gut 1986; 27:1029-34.

Kararli, TT. Comparison of the gastrointestinal anatomy, physiology, and biochemistry of humans and commonly used laboratory animals. Bipharm Drug Dispos 1995;16:351-80.

Lorkowski, G. Gastrointestinal absorption and biological activities of serine and cysteine proteases of animal and plant origin: review on absorption of serine and cysteine proteases. *Int. J Physiol Pathophysiol Pharmacol* 2012; 4:10-27.

Paganelli R, Levinsky RJ. Solid phase radioimmunoassay for detection of circulating food protein antigens in human serum. *J Immunol Methods* 1980; 37:333–41.

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Expert Report of Richard P. Bazinet, Ph.D.

Transcript of the deposition of Dr. Richard Bazinet, Oct. 16, 2015.

EXHIBIT D

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NORTHERN CALIFORNIA

PHILLIP RACIES, On Behalf of Himself and All Others Similarly Situated, Plaintiff, vs. QUINCY BIOSCIENCE, LLC, Defendant.	Case No. 3:15-cv-00292-HSG **EXPERT REPORT OF WILLIAM BISORDI, M.D., F.A.C.P.**

EXPERT REPORT OF WILLIAM BISORDI, M.D., F.A.C.P.

I. INTRODUCTION.

1. I, William Bisordi, M.D., FACP, submit this expert report at the request of Quincy Bioscience, LLC ("Quincy"), defendant in the above-captioned litigation.

2. The opinions expressed in this Report are subject to amendment, supplementation or modification based on information made available to the parties in the case, or to respond to or rebut issues, statements and opinions advanced by the plaintiff Phillip Racies ("Racies" or "Plaintiff") or Plaintiff's witnesses.

3. If called upon, I am prepared to testify about my background, qualifications, and experience as well as about the issues and opinions described in this Report. Furthermore, I anticipate that I may be asked to provide testimony and to consider and respond to arguments that Plaintiff's expert(s) or fact witnesses may raise at any hearing, in reports, and/or at trial.

A. My Background and Qualifications.

4. A copy of my updated *curriculum vitae* is attached as Exhibit A and includes details of my educational, professional, research and employment credentials.

5. I received a Bachelor of Science Degree in Biology from Manhattan College in Riverdale, New York, in 1969, and an M.D. from St Louis University College of Medicine in 1973.

6. I have been practicing medicine for more than 35 years, and am currently certified by the American Board of Internal Medicine, and the American Board of Gastroenterology. I am a Fellow (Life Member) of the American College of Physicians, a Senior Member of the American Gastroenterological Association, and a member of the American Society of Gastrointestinal Endoscopy.

7. I previously served as a Clinical Assistant Professor of Medicine at New York Medical College, on the Board of Directors of the Westchester Medical Center and as the Chief of Gastroenterology of Sound Shore Medical Center.

8. At present, I am a Hearing Board Member of the New York State Department of Health Office of Professional Medical Conduct and have held that position since 2003.

B. Prior Testimony and Compensation.

9. During the past four years, I have provided expert testimony at trial in the following cases:

- *Alberici v. Wolfson, M.D.*, Kings Supreme Court, NY, Case #026286/2011 (testified in 2014);
- *Fasulo v. Vento*, Kings Supreme Court, NY, Case #16189/2010 (testified in 2014);
- *Estate of Richard Willis v. Paula Bailey, M.D. and Steven Shedlovsky, M.D.*, Fayette, KY Circuit Court Division 4, KY, Case #09-C1-1950 (testified in 2013);
- *Ideliza v. Solano*, New Britain, CT, Case # CV-07-5006287-S (testified in 2012).

10. I am being compensated at my customary rate of $400/hour for my work on this matter. My compensation does not depend in any way on the outcome of this case.

C. Materials Considered and Preparation.

11. The opinions and the statements I make in this Report are based on my knowledge, expertise and professional experience. In addition, I rely on and incorporate by reference the documents and information cited in the Report itself and listed in Exhibit B.

II. OPINIONS.

A. Legal Understanding.

12. I reviewed the Court's Order denying in part and granting in part Quincy's Motion to Dismiss Racies' Complaint. My understanding is that the Court dismissed any claims that are based on any "lack of substantiation" of the benefits of taking Prevagen®. The Court allowed some claims to proceed, and ordered the Plaintiff to "affirmatively prove the falsity of Defendant's Product claims." (D.I. 34 at 6).

13. The Court quoted Plaintiff's allegations:

> (1) [the Product] cannot work as represented because apoaequorin, the only purported active ingredient in [the Product], is completely destroyed by the digestive system and transformed into common amino acids no different than those derived from other common food products . . . : (2) the average daily diet contains about 75 grams of protein, contains all the required amino acids, and has about 7,500 times more amino acids than [the Product] (10 mg or 0.01 grams) and, as a result, any amino acids derived from the digestion of [the Product] would be massively diluted and could have no measurable effect on the brain; (3) ingestion of [the Product] cannot and does not have any effect on brain function or memory."

(Id.)

14. The Court then Ordered Plaintiff to "successfully prove that the apoaequorin in the Product is destroyed by the human digestive system or is of such a trivial amount that it cannot biologically affect memory or support brain function." (*Id.*).

B. Plaintiff's Expert Dr. Richard Bazinet's Statements Contradict Plaintiff's Allegations.

15. I have reviewed the expert report of Dr. Richard Bazinet, an expert witness retained by Plaintiff, and the transcript of Dr. Bazinet's deposition of October 16, 2015. Neither Bazinet nor the Plaintiff provided any evidence that can affirmatively

prove, as the Court required them to do, that apoaequorin in Prevagen is "destroyed" by the human digestive system or is of such a "trivial" amount that it cannot carry out some effect in humans.

16. As the Court noted, Plaintiff has alleged that (1) "Prevagen *cannot* work because apoaequorin is *completely* destroyed by the digestive system and transformed into *common amino acids*"; and (2) "*any amino acids* derived from the digestion of Prevagen would be massively diluted and could have no measurable effect on the brain."

17. Upon my review, it is my professional opinion that Dr. Bazinet did not provide any evidence whatsoever to show that apoaequorin is "completely" digested to "common amino acids," in a human body or otherwise. Dr. Bazinet actually stated in his expert report that "before aqoaequorin even enters the intestine it has been reduced down to amino acids *and possibly some small peptides.*"

18. As discussed further below, amino acids and "small peptides" are two different things. Therefore, Dr. Bazinet's statement that apoaequorin is reduced to small peptides contradicts Plaintiff's first allegation that "Prevagen *cannot* work because apoaequorin is *completely* destroyed by the digestive system and transformed into *common amino acids*."

19. Dr. Bazinet admits that he has done no testing of apoaequorin and that he has not run any digestion studies. (Dep. Tr. at 33). During his deposition, Dr. Bazinet again confirmed that "Proteins are broken down into amino acids *and some small peptides in some cases*. And those are how we absorb proteins, actually." (Dep. Tr. at 110; *see also id.* at 141-42). Specific to apoaequorin, Dr. Bazinet testified he had *no evidence* that it is entirely digested into single amino acids. (Dep. Tr. at 121). Dr.

Bazinet also testified that "small peptides can enter the blood" after protein ingestion. (Dep. Tr. at 138-39)

C. Scientific and Medical Evidence Supports That Proteins and Peptides Can Enter the Blood Stream after Human Ingestion.

20. Dr. Bazniet admitted that he had never worked on apoaequorin outside the context of this litigation. He never ran any tests on apoaequorin. His opinions on how apoaequorin would be digested in a human body are largely an extrapolation of what he believed to be a general principle that "all" proteins would be digested into amino acids and therefore have no effect in the body. (Dep. Tr. at 109). Dr. Bazinet's opinion is wrong. Indeed, he admits that peptides can enter the blood stream after being ingested on more than one occasion. (Dep. Tr. at 110, 139). He also states that proteins vary on how much they are digested to peptides and amino acids. (Dep. Tr. at 259).

21. A review paper by Michael Gardner published in 1988 in the Annual Review of Nutrition stated (a) "it is commonly assumed that dietary proteins are digested completely to free amino acids within the lumen of the gastrointestinal tract before absorption occurs, or (b) that only trace amounts of macromolecular fragments enter the circulation and that these are of absolutely no nutritional, physiological, or clinical relevance. The first of these assumptions is blatantly untrue. It is now known that intestinal peptide transport is a major process with the terminal stages of protein digestion occurring intracellularly after transport of peptides into the mucosal absorptive cells. Also, there is now irrefutable evidence that small amounts of intact peptides and proteins do enter the circulation under normal circumstances. Intact protein absorption must now be regarded as a normal physiological process in humans and animals." (Gardner 1988, at 329, 330).

22. Another paper observed "Within the last four decades the view on the absorption of high molecular weight molecules (e.g. proteins and peptides) across the gastrointestinal barrier has completely changed. It is now accepted beyond reasonable doubt that significant (albeit small) amounts of macromolecules can be absorbed in intact and biologically active form." (Lorkowski 2012, at 13).

23. Castell et al. conducted a study that concluded that bromelain, a mixture of proteins extracted from pineapple stem, can enter the blood of healthy human subjects *as full-length proteins* after it is ingested. Bromelain is a digestive enzyme and freely crosses the gut without toxicity or allergenicity and without losing its activity. It possesses fibrinolytic, anti-edematous, anti-thrombotic, and anti-inflammatory activities. Castell's group detected ingested bromelain in the blood by an immunoassay. Half-lives of circulating bromelain were established for up to nine hours in healthy male subjects taking three grams per day of the enzyme.

24. According to the Castell et al. study discussed above, the major protein component of bromelain in the blood appears to be about 24 kiloDaltons (kDa), which I understand corresponds to the full-length proteins in bromelain. Thus, it can be concluded that full-length proteins are present in the blood. Coincidentally, the size of bromelain is similar to the size of apoaequorin (about 21 kDa). (Castell 1997, at G143; *see also* Maurer 2001, at 1241).

25. Castell et al. showed that ingested bromelain can reach a blood concentration of as high as 9.8 ng/ml. (Castell 1997, at G142 Table 1). This data conclusively refutes the false premise Dr. Bazinet relied on, which is that all dietary proteins are digested into amino acids.

26. Ero et al. reported that Nattokinase, a 27.5 kDa serine protease has been shown to enter the body systemically to effect the degradation of fibrinolytic proteins involved in clotting in the serum. Nattokinase is detected directly in the bloodstream of its users. A 2013 study demonstrated the pharmacokinetics of a single capsule (100 milligrams) of Nattokinase. The peak concentration for the protein was obtained at an average of 13.3 hours over a 48 hour assay when 11 persons age 21- 65 took the capsule. (Ero et al 2013).

D. Numerous Studies, Including Randomized, Controlled Clinical Studies in Humans Have Shown That Ingested Proteins or Peptides Can Have a Biological Effect.

24. Set forth below is a summary of multiple controlled clinical trials with bromelain (Maurer 2001, at 1243 Table 5):

Table 5. Selection of controlled clinical studies with bromelain.

Diagnosis	Design of study	*n*	Drug, daily dosage	Critical parameters, results, observations	Ref.
Acute sinusitis	r, db, Pl	V : 23 Pl : 25	4 × 40 mg Br	inflammation, secretion, breathing, disturbance, pain. V significantly better than Pl	25
Face and head trauma	db, Pl	V : 20 Pl : 21	4 × 40 mg Br	edema, ecchymoses; reduction by V highly significant	19
Trauma of lower extremity	r, b, Cd	V : 18	3 × 40 mg Br 3 × 1000 mg Cd	pain, edema, hematoma. V significantly better than oxyphenbutazone (Cd)	80
Posttraumatic inflammation and swelling	r, b, Cd	V : 60 Cd : 60	3 × 40 mg Br 3 × 1000 mg Cd	hematoma, edema, flexibility, pain; equivalence of V and oxyphenbutazone (Cd)	81
Postoperative tumefactions	r, db, Pl	V : 50 Pl : 50	3 × 80 mg Br	girth of ball of forefoot, smallest girth of forefoot pain intensity; significant improvement of all parameters by V	82
Mediolateral episiotomy	r, db, Pl	V : 80 Pl : 80	4 × 40 mg Br	edema, inflammation, pain; V significantly better than Pl	83
Oral surgery (teeth extraction)	r, db, cr	16	4 × 40 mg Br	swelling, pain; less inflammation and pain by V	84

n, number of patients; r, randomized; db, double-blind; cr, cross-over; Pl, placebo; Cd, control drug; Br, bromelain; V, verum.

25. In multi-center, double-blind, randomized studies, ingested serrapeptase was shown to reduce inflammation (Tachibana 1984; Mazzone 1990). In both the Tachibana and the Mazzone studies, patients took 30 mg of the protein daily, an amount similar to the amount of apoaequorin one would get from Prevagen, which is 10 or 20 mg per day. In an open-labeled trial, serrapeptase reduced mucus in patients (Nakamura 2003).

26. In other research, therapeutic approaches have involved the blend of plant and animal hydrolytic enzymes. This treatment has been used to reduce swelling and advance healing of patients undergoing jaw surgeries as tested in a double-blind, randomized, placebo-controlled clinical trial (Shetty, 2013).

27. Therefore plaintiff's expert witness, Dr. Richard Bazinet, is mistaken in his belief that all proteins entering the gastrointestinal tract are hydrolyzed to constituent amino acids, and that apoaequorin would be destroyed before uptake would effect a physiological response. He goes to lengths to assert that proteins and peptides differ but does not discuss how they differ. Peptides are small proteins and most often linear as opposed to globular: that is the only significant scientific difference. Peptides are understood to be fragments of larger polypeptides. All secreted proteins are, in fact, fragments of larger polypeptides and many secreted proteins, as well as intracellular proteins, have no function until they are fragmented into smaller polypeptide entities, i.e., peptides.

28. It is well known proteins could become biologically active in the human gastrointestinal tract after hydrolysis into smaller fragments. In a recent paper, over 134

peptides were identified as angiotensin-I converting enzyme inhibitors. A partial list of these peptides was given in the table below (Agyei, 2015):

Table 1. Some examples of soy-derived peptides and their bioactive properties.

Identified Peptide / Amino Acid Sequence	Bioactive Properties	Description of Bioactivity	Mode of Production and Isolation /Purification	Ref.
Peptides from glycinin and β-conglycinin	Antimicrobial properties	Peptides inhibited the growth of *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Salmonella enterica, Klebsiella pneumoniae, Streptococcus mutans* and *Propionibacterium acnes*	Pepsin hydrolysis and dialysis (3,500 kDa cutoff membrane)	[10]
Peptides from glycinin and β-conglycinin	Antioxidative	Scavenging of ABTS and DPPH radicals; and inhibition of β-carotene oxidation	Pepsin hydrolysis and dialysis (3,500 kDa cut-off membrane)	[10]
Soy aglycin (peptide with 37 amino acid residues)	Antidiabetic	Improvement in oral glucose tolerance ; control of hyperglycemia; increase in insulin receptor signalling pathways in diabetic mice	Not reported	[11]
Peptides from β-conglycinin (Leu-Leu-Pro-His-His)	Antioxidative	Inhibition of linoleic acid auto-oxidation in an aqueous system	Hydrolyses with protease S, and purification by gel filtration and reversed-phase HPLC	[12, 13]
Low molecular weight peptides (NMWCO < 3 kDa)	Antioxidative	Lipid peroxidation inhibition	Alcalase hydrolysis of soy proteins, and purification by ultrafiltration, gel filtration and reversed-phase HPLC	[14]
Protein hydrolysates with MW of 10–50 kDa	Anticancer	Inhibition of human colon, lung and liver cancer cells	Alcalase hydrolysis of soy protein isolate, and purification by reversed-phase HPLC	[15]
Lunacin	Anti-inflammatory; Antioxidative; Antihypertensive	Various multifunctional properties	Solvent extraction and ion-exchange and reverse-phase chromatography	[16, 17]
Lunacin	Anticancer	Topical application of lunasin causes chemopreventive effects against skin tumors in SENCAR mice	Recombinant DNA technology	[18]
Met-Leu-Pro-Ser-Try-Ser-Pro-Try	Anticancer	Antimitotic properties	Thermoase hydrolysis of soy proteins, and purification by solid phase extraction and HPLC	[19]
Natto hydrolysates with Phe-Phe-Tyr-Tyr and Trp-His-Pro sequences	Antihypertensive peptides	Inhibition of ACE	Hydrolysis by bacterial neutral protease	[20]
Soy protein hydrolysates containing Leu-Ile-Val-Thr-Gln sequences	Antihypertensive peptides	Inhibition of ACE	Fermentation of soy proteins by lactobacilli	[21]
Soy morphin-5 (Tyr-Pro-Phe-Val-Val)	Opioid	Anxiolytic (anxiety relieving) properties in mice	Fmoc peptide synthesis	[22]
Soymetide (Met-Ile-Thr-Leu-Ala-Ile-Pro-Val-Asn-Lys-Pro-Gly-Arg)	Immunostimulating	Increased phagocytosis by human polymorphonuclear leucocytes; Activity chemotherapy-induced alopecia in mice	Trypsin hydrolysis of β-conglycinin, and ion-exchange purification, reversed-phase HPLC	[23, 24]
Ethanol soluble soy protein hydrolysates	Hypocholesterolemic	Cholesterol lowering properties via stimulation of low-density lipoprotein receptor transcription in human liver cell lines	Hydrolysis by neutral proteases from *Bacillus amyloliquefaciens* FSE-68; and ethanol extraction	[25]

ABTS, 2,2'-azino-bis-3-ethylbenzthiazoline-6-sulphonic acid; DPPH, 1,1-diphenyl-2-picrylhydrazyl; HPLC, high performance liquid chromatography; NMWCO, nominal molecular weight cut off; ACE, angiotensin converting enzymes; Fmoc, fluorenylmethyloxycarbonyl chloride.

29. As reflected in the table above, food can be a natural source of bioactive peptides due to the hydrolytic processes that occur during gastrointestinal digestion.

E. Plaintiff's Second Allegation, That "*Any Amino Acids* Derived from the Digestion of Prevagen Would Be Massively Diluted and Could Have No Measurable Effect on the Brain," Also Lacks Support.

30. As discussed above, Racies or Dr. Bazinet provided no evidence that apoaequorin is digested all the way down to single amino acid after ingestion by humans. The "dilution" allegation has no support when an ingested protein is not digested to single amino acids.

31. The discussion above provided some examples of bioactive peptides that are specific portions of proteins with between two and twenty amino acids. They are different from amino acids with respect to "dilution," because the number of different types of peptides is exponentially larger than the number of different types of amino acids. The administration of some types of peptides can have a therapeutic effect, and certainly a biological effect, when introduced into the human body. The ingested peptides are not "diluted" by or equivalent to peptides that can be generated by other dietary proteins.

32. For example, peptides consisting of two to six amino acid residues were identified as ACE inhibitors by administration to rats. (de Castro 2015, at 194). The point is that some ingested peptides do not simply provide nutrition—they are bioactive and not "diluted" by other dietary proteins or the proteins in an animal's body. Dr. Bazinet states that "all dietary proteins are digested into amino acids. There's not one

exception." (Dep. Tr. at 120). This is clearly not the case as proteins can be broken down into peptides, some of which can be bioactive.

III. CONCLUSION.

33. Regardless of the exact mechanism of absorption or action, the relevant studies cited herein show that ingested proteins, or some parts of them, are absorbed by the human body, resulting in a measurable effect. The results from these studies refute the notion that all ingested proteins are digested in humans to indistinguishable and "diluted" amino acids and cannot have a measurable effect in the body. To the contrary, these published studies show that proteins, when ingested in the milligrams-range, can and do have a biological effect in humans.

I declare under penalty of perjury that the foregoing is true and correct to the best of my knowledge.

Dated: November 9, 2015

William Bisordi, M.D., F.A.C.P.

Exhibit A

To the Expert Report of

Dr. William Bisordi, M.D., FACP

Curriculum Vitae

William Bisordi, MD, FACP
151 Rockland Ave.
Larchmont, NY 10538
phone/fax 914 834 8426

DATE OF BIRTH: 11/13/1947

PLACE OF BIRTH: Mt. Vernon, N.Y.

MEDICAL LICENSURE: New York State

CERTIFICATION:

American Board of Internal Medicine, 1976
American Board of Gastroenterology, 1977
National Board of Medical Examiners, Diplomate 1974
Recertified 1992

EDUCATION:

Medical School:
St. Louis University School of Medicine, 1969-1973
College:
Manhattan College, Riverdale, N.Y., 1965-1969
B.S. (Biology)

POSTGRADUATE TRAINING:

Fellowship:
Gastroenterology, Strong Memorial Hospital, University of Rochester, N.Y. 1975-1977
Residency:
Internal Medicine, Cornell University Cooperating Hospitals
New York, N. Y. 1973-1975
Internship:
Internal Medicine, Cornell University Cooperating Hospitals
New York, N. Y. 1973-1974

APPOINTMENTS:

Fellow (Life Member) American College of Physicians, 1978- present
Clinical Assistant Professor of Medicine, New York Medical College, 1992-2003
Board of Directors, Westchester Medical Center, 1997-2003
Chief of Gastroenterology, Sound Shore Medical Center, 1991-1992
Attending Physician, Sound Shore Medical Center, 1977-1994
Attending Physician, Mt. Vernon Hospital, 1977-1994
Chairman Quality Care Committee, Westchester Medical Center, 1998-2003
Medical Malpractice Committee, Westchester Medical Center, 1998-2003

Westchester County Health Care Corporation Board Liaison to New York Medical College Board of Trustees 1998-2003
Executive Performance Improvement Committee, Westchester Medical Center, 1998-2003
Board of Directors, Hemophilia Association of New York, 1998-2001
Medical Affairs Chairman, Westchester Hemophilia Committee, 1977-2001

AWARDS:

American Medical Association Physician's Recognition Award for Continuing Medical Education, May 1 2011- May 1 2012

PROFESSIONAL SOCIETIES:

American College of Physicians, Fellow, Lifetime Member, 1978- present
American Gastroenterological Association, Senior Member, 1978- present
American Society of Gastrointestinal Endoscopy, 1978- present

PUBLICATIONS:

Bisordi WM, Lightdale CJ. Discordancy of ulcerative colitis in identical twins. American Journal of Digestive Diseases. January 1976
Bisordi WM, Lightdale CJ. Menetrier's Disease and carcinoma of the pancreas. American Journal of Gastroenterology. January 1976
Bisordi WM, Kleinman MS. An improved snare for removal of rectosigmoid polyps. American Journal of Digestive Diseases. December 1976
Bisordi WM, Kleinman MS. Melanosis duodeni. American Journal of Gastrointestinal Endoscopy. May 1976

CAREER EXPERIENCE:

New York State Department of Health Office of Professional Medical Conduct, Hearing Board, 2003- present

Board of Directors, Secretary, Westchester Health Care Corporation, 1998-2003

Expert Medical Record Review, for plaintiff and defense cases, 1992- present

Medical Director, Care Plus Health Plan, 1995-1997

Senior Physician Consultant, Island Peer Review Organization, 1992-1998

Private Practice, Gastroenterology, 1977-1994

Exhibit B

To the Expert Report of

Dr. William Bisordi, M.D., FACP

Additional Materials Considered

JOURNAL ARTICLES

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Brown, R. C., Calcium Modulation of Adherens and Tight Junction Function A Potential Mechanism for Blood-Brain Barrier Disruption After Stroke. Stroke. 2002;33:1706-1711.

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OTHER DOCUMENTS:

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EXHIBIT E

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UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

PHILLIP RACIES, On Behalf of Himself and All Others Similarly Situated, Plaintiff, vs. QUINCY BIOSCIENCE, LLC, a Wisconsin limited liability company, Defendant.	Case No. 3:15-cv-00292 HSG **EXPERT REPORT OF BRIAN SPENCER, PH.D.**

Introduction

1. I, Brian Spencer, Ph.D., submit this report (this "Report") at the request of Quincy Bioscience, LLC. ("Quincy") in the above-captioned litigation.

2. The opinions expressed in this Report are subject to amendment, supplementation, and/or modification based on information made available to the parties in the case and/or to rebut issues, statements, and opinions advanced by Plaintiff Phillip Racies ("Racies" or "Plaintiff") or his witnesses.

3. If called upon, I am prepared to testify about my background, qualifications, and experience as well as the issues and opinions described in this Report. Furthermore, I anticipate that I may be asked to provide testimony and to consider and respond to arguments Plaintiff's expert(s) or fact witnesses may raise at hearings, in reports, and/or at trial.

Background and Qualifications

4. A copy of my most-recent *curriculum vitae* is attached hereto as Exhibit "A" and includes details of my educational, professional, research, and employment credentials.

5. I received a Bachelor of Science in Bacteriology from the University of Wisconsin in 1994. I then received my Ph.D. in Medical Microbiology and Immunology at the University of Wisconsin in 2000 where I studied the delivery of growth factors to photoreceptor cells, a highly specialized neuron of the eye, to prevent retinal degeneration.

6. After receiving my Ph.D., I moved to the Salk Institute for Biological Studies to work with Inder Verma, Ph.D. to investigate the delivery of therapeutic proteins across the blood-brain barrier ("BBB") for the treatment of neuronal degenerative diseases. This research lead to a major advance in the field, publication in The Proceedings of National Academy of Science, 2 patent applications and the Cozzarelli Prize for scientific excellence in the medical field in 2008.

7. I then received a position at the University of California, San Diego working with Eliezer Masliah, M.D. to deliver therapeutic proteins across the BBB for neurodegenerative disorders such as Alzheimer's and Parkinson's diseases. In addition, I have established collaborations with numerous researchers in the field to investigate the genetic causes of Alzheimer's and Parkinson's Diseases. These collaborations have led to over 55 peer reviewed publications and another patent.

8. In 2008, I formed NeuroTransit, Inc, to develop therapies for Alzheimer's and Parkinson's using the techniques I developed for delivering proteins across the

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BBB. During this time, I took several classes in pharmacology and became ADMET certified through the University of California, San Diego Extension.

9. In 2005 I organized a hands-on scientific symposium for the California Bar for the California Science and Law Conference. I have refereed several papers and grants in the area of neuroscience and currently serve as an associate editor of the Journal of Neurodegenerative Diseases.

Prior Testimony and Compensation

10. I have not testified in deposition or at trial in the previous four years.

11. I am being compensated for my work on this matter at the rate of $100.00 per hour for non-testifying work and at the rate of $450.00 per hour for testifying at deposition or trial. My compensation is not contingent on my opinion and does not depend on the outcome of the case.

Materials Considered

12. The opinions and statements I make in this Report are based upon my knowledge, expertise, and professional experience. In addition, I rely and incorporate by reference the documents and information cited in this Report and listed in Exhibit "B".

Summary of Opinions

13. Prevagen, manufactured by Quincy Biosciences, LLC, is an over the counter oral supplement designed to improve memory. The main dietary ingredient in Prevagen is Apoaequorin ("AQ"), a 22kDa calcium binding protein, which was originally discovered for its bioluminescence properties in the jellyfish, *Aequoria victoria*, and now developed through recombinant fermentation process. Evidence provided by Quincy in the document file describe several examples of AQ affecting neuronal survival and behavioral changes. Quincy has documented increased neuronal cell survival and memory improvements following direct delivery of AQ to the brain as well as through oral administration.

14. Such neuronal and behavioral changes lead me to believe that AQ has an effect on the brain; however, the data presented do not provide sufficient evidence to

determine an exact mechanism for this effect. I have been asked to provide my opinion as to whether it is impossible for AQ to pass the BBB. In my opinion, it is not impossible for AQ to pass the BBB and have an effect on brain chemistry.

15. Based upon my background in neuroscience and delivery of proteins and peptides across the blood-brain barrier I have developed four hypotheses to explain why it is not impossible for an oral delivery of AQ to pass the BBB and/or affect brain chemistry. These include; 1) receptor mediated trancytosis, 2) cell penetrating peptide, 3) "sink" hypothesis, and 4) "leaky" BBB. I will detail each of these below.

AQ Could Pass Through the BBB via BBB Trancytosis

16. The BBB controls the passage of substances from the blood into the central nervous system ("CNS"). Thus, a challenge for the delivery of protein therapeutics is the transport of large proteins to the CNS. The BBB is composed of tight junction-forming endothelial cells, pericytes, and astrocytes. This combination functions to allow only small molecules and directed transport by receptor-mediated trancytosis from the blood to the CNS.

17. For instance, transport of iron by the protein transferrin occurs via the transferrin receptor and transport of lipids occurs via the proteins apolipoproteins via the lipoprotein receptors. This occurs by binding of the protein to the receptor on the blood side of the endothelial cell, internalization and transport to the neuronal side, followed by exocytosis of the protein and release from the receptor. The receptor is then recycled back to the blood side of the endothelial cell. Many investigators have utilized this natural mechanism to transport proteins across the BBB that are not normally transported to the CNS.

18. This process can be co-opted by utilizing an antibody to the receptor and attaching the cargo protein, thus piggy-backing on the receptor-mediated transport. In 1991, Starzyk et al were the first to show that targeting a receptor on the blood-brain barrier could transport a "cargo" protein to the neuronal side of the BBB [1]. An antibody developed against the transferrin receptor expressed on the blood-brain barrier

was able to transport methotrexate to the CNS. This same approach has been used to target the transport of proteins and peptides across the BBB efficiently [2, 3].

19. Alternatively, the process can be co-opted by utilizing as little as the receptor-binding domain of the target protein. These targeting peptides can be as small as 19 amino acids or fewer [4-8]. Thus, binding to the receptor on the endothelial cell is sufficient to trigger endocytosis and trancytosis to the neuronal side. In fact, delivery of naked nanoparticles has been found to be transported to the CNS without the addition of any targeting molecules such as antibodies or receptor binding domains [9, 10]. This BBB trancytosis occurs by non-specific "sticking" to apolilpoproteins in the serum that then themselves bind the LDL-receptor at the BBB and transcytose the whole complex to the neuronal side.

20. Therefore, contrary to the conclusions reached by Plaintiff's expert in this case that AQ cannot pass the BBB, it is possible for AQ to pass the BBB by binding to any of the receptors on the BBB either on its own or in association with a serum protein that itself can bind and trigger trancytosis. Dr. Bazinet fails to rule out BBB trancytosis, nor could he rule it out without completing extensive *in vitro* and *in vivo* analysis of AQ in a controlled environment of the BBB.

AQ Could Pass Through the BBB via Cell Penetrating Peptides

21. Cell penetrating peptides are short stretches of amino acids ranging from approximately 8 to 28 amino acids in length [11]. These peptides transit into and out of cells across the lipid bilayer in a receptor independent manner. These peptides were first identified in 1998 with the characterization of the HIV protein TAT. To date these peptides have been isolated from a variety of source proteins including: virus, bacteria, insect, mammal and even synthetically generated [11]. With little in common among the various peptides, there is no method for identifying future cell penetrating peptides that may occur in proteins other than through experimental testing.

22. Several cell penetrating peptides have been utilized to deliver proteins across the blood-brain barrier following intra-venous delivery distribution [12-14]. In fact, addition of a cell penetrating peptide can facilitate the absorption of proteins

across the small intestinal epithelium [15]. Thus, experimental evidence exists for the presence and use of cell penetrating peptides for non-specific transport of proteins from the gut to the blood and from the blood to the brain.

23. Dr. Bazinet's expert report and opinions fail to rule out the possibility that AQ contains a cell penetrating peptide that allows it to pass through the BBB. Cell penetrating peptides are continuing to be identified as this is a relatively new field in brain chemistry and, based upon my review of Dr. Bazinet's report and material in support thereof, he does not provide sufficient information and has not conducted the appropriate studies to determine whether AQ does or does not contain such a peptide.

AQ Could Affect Brain Chemistry Under "Sink" Hypothesis

24. One common hypothesis for the method of action for proteins that are not thought to enter the brain but appear to have a measurable effect either through neuronal chemistry, neuronal survival or change in behavior is called the "sink" hypothesis [16, 17]. Under this hypothesis, the mode of action of a therapeutic protein occurs outside the brain, altering the chemistry or the levels of a protein on the blood side of the blood-brain barrier. Then by the process of achieving equilibrium, the blood-brain barrier reduces the accumulated protein or offensive chemistry in the brain, flushing it to the blood. Thus the blood acts as a "sink" and the therapeutic protein or drug activity occurs solely in the blood. Plaintiff's expert has not ruled out the possibility that AQ does not even need to enter the brain to affect an action directly on brain chemistry. This could occur directly in the blood via the "sink" hypothesis.

25. Finally, AQ may not be acting directly on the brain at all. The protein may be acting through another system or signaling complex that has not been identified in the studies performed to date. Plaintiff's expert has not ruled out that AQ could be acting on another organ such as the liver or kidney and thus inducing the release of signaling peptide or proteins that themselves enter the brain and affect brain chemistry or neuronal survival. These hypotheses would need further testing to confirm or rule out and based upon my review of Dr. Bazinet's expert report and accompanying documents, he has not conducted sufficient testing to rule out this possibility.

AQ Could Pass the BBB Through "Leaky" Barriers

26. In healthy individuals and animal models, the BBB will exclude most proteins and small molecules from entering the brain except in the circumstances described above. However, in aged individuals or those with neurodegenerative disorders, the BBB has been known to become "leaky". This means that the endothelial cells that normally provide very tight junctions and prevent the passage of peptides and proteins begins to separate and allow the non-specific passage of proteins to the brain.

27. This has been documented in both animal models of Alzheimer's disease [18] [19] as well as older healthy individuals [20] and those with Alzheimer's disease [20] [21] [19] [22] [23]. In fact in some patients with hypertension and diabetes, BBB disruption has been detected by the passage of the blood protein albumin across the BBB into the cerebral spinal fluid [22] [24]. Over 5 million Americans have Alzheimer's disease [25] and the incidence of diabetes is 7 in 1000 Americans [26] so the prevalence of a "leaky" BBB is not as rare as Dr. Bazinet contends in his opinions. The serum protein albumin found in the brain in these aged and/ or diseased individuals is 66 kDa, 3 times larger than AQ at 22 kDa, so it is reasonable to believe that in cases of "leaky" BBB, AQ could pass from the blood to the brain as a whole protein.

Examination of Remaining Documents

28. First order pharmacokinetic analysis of the delivery of a substance of interest typically involves a single bolus delivery of the substance followed by analysis at several time points at the target tissue. In the study of AQ in rats, dogs or humans, this would have involved the single oral dosage at time point zero probably by oral gavage in order to deliver the whole amount at once. Then in the case of the laboratory animals, the blood, CSF, and brain would have been analyzed at various terminal time points to determine how much protein entered which space, the half-life of the protein, the clearance rate and the accumulation. The documents provided do not show that these studies were completed so Dr. Bazinet cannot speculate on the uptake, clearance, and accumulation of the Apoaequorin as it relates to time or dosage.

29. This is important when reading the data presented in the poster titled "Orally administered Apoaequorin protects neurons from oxygen-glucose deprivation" by Adams et al. on QUI873. In this study, rats received oral administration through their daily diet of either AQ or a control.

30. Two different studies were conducted for this poster. In the first study, rats received 5 mg/kg of AQ or control for 7 or 30 days. This study was conducted to determine whether AQ when administered for 7 or 30 days could be protective in an *ex vivo* oxygen/glucose model of ischemia. The question examined here is time following continuous administration for AQ to be effective in the brain.

31. The second experiment performed in this poster involves the administration of various oral doses of AQ through daily diet to the rats of 0, 3.6, 48, 240 or 480 mg/kg. At the final time point, the rats were sacrificed and brains were examined in the same *ex vivo* oxygen/ glucose model of ischemia. In addition, brains were examined for the presence of AQ by western blot using an antibody that had been previously developed against AQ. This study is designed only to examine the dose response protective effect of AQ at one time point and only to examine the remaining AQ in the brain at that one time point. Thus, it is not a pharmacokinetic study and, Dr. Bazinet's attempts notwithstanding, conclusions on the absorption and clearance of AQ cannot be made from the data presented here.

32. Both studies performed on the rats make use of the *ex vivo* oxygen/ glucose ischemia model. This is a common model performed in laboratory to examine neuronal survival during an insult of oxygen and glucose starvation [27]. Importantly, this model is well recognized and reproducible. Following oxygen/ glucose starvation, the brain sections are stained with trypan blue in order to identify the dead or dying cells. Again, this is a common method for differentiating live cells from dead or dying cells. The dye, trypan blue, is excluded from live cells by the lipid bilayer membrane, whereas, dead or dying cells cannot exclude the dye and instead stain blue. Counting decreased numbers of blue cells indicates a resistance to the conditions presented in the oxygen/ glucose ischemia experiment suggesting that AQ is acting to prevent neuronal

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cell death in the CA1 region of the hippocampus. Incidentally, this is the region of the brain most susceptible in Alzheimer's disease.

33. Figure 5 of the poster shown in QUI873 shows that administration of AQ for 7 days has a significant protective effect in the *ex vivo* oxygen/ glucose ischemia model. The first two bars of the graph are the controls in the experiment. The first bar represents the cell death results from rats that received no AQ and were not subjected to oxygen/ glucose starvation. These would be the negative or normal control. The next bar represents the cell death results from rats that received no AQ and were subjected to the oxygen/ glucose starvation. These would be the positive or worst case control. The next bar represents rats that were treated with AQ for 7 days and then not subjected to oxygen/ glucose starvation. This shows that treatment with AQ does not increase or decrease the number of trypan blue staining cells on its own as the bar is similar to the negative control. Finally, we have those rats that were treated with AQ for 7 days and then subjected to oxygen/ glucose starvation. We see from this bar that there is significant neuronal protection in the ischemia assay. This was not carried over to the rats treated with AQ for 30 days, however that issue is addressed in the following section.

34. Figures 6 and 7 of the poster show the results from the dose response at the final time point investigating the neuronal survival in the same ischemia model as well as the presence of AQ in the brain by immunoblot analysis. Figure 6 shows significant protection of neurons in the hippocampus following the oxygen/ glucose ischemia model in those animals that received 48 mg/kg of AQ daily but not in those animals that received 3.6, 240 or 480 mg/kg of AQ. Again, this figure is measuring the numer of trypan blue cells that represents dead or dying cells following the oxygen/glucose ischemia model assay.

35. Figure 7 shows by western blot the presence of AQ in whole brain homogenates from rats that received the 48 mg/kg daily dose of AQ; however, AQ was not detected in animals that received doses of 240 or 480 mg/kg. The western blot was

visualized with a chemiluminescent reagent as mentioned in the Methods section of the posted, not with the trypan blue as Dr. Bazinet mistakenly suggested in his deposition.

36. In summary, the *ex vivo* ischemia model shows a neuroprotective effect from oral administration of Apoaequorin at doses of 5 mg/kg (Figure 5) and 48 mg/kg (Figure 6) and the immunoblot shows the presence of Apoaequorin in the brain following the oral administration of 48 mg/kg (Figure 7). However, there does not appear to be a neuroprotective effect following administration of 3.6, 240 or 480 mg/kg, nor were the authors able to detect AQ in the brain following administration of Apoaequorin at 240 or 480 mg/kg. In my experience with therapeutic delivery of a foreign protein (e.g. not originally made in the animal) there is always the possibility of eliciting an immune response that can lead to clearance. This occurs at some point, usually a few days to a week after the initial delivery of the protein, and leads to a loss of therapeutic effect. We could develop a hypothesis wherein the lowest dose utilized, 3.8 mg/kg, is too low to elicit a neuroprotective effect. Doses of 5 and 48 mg/kg elicit a neuroprotective effect and are low enough to evade an immune response. However, doses of 240 and 480 mg/kg are high enough to elicit and immune response in the rat, leading to clearance from the blood stream and a loss of therapeutic effect. This could be through increased concentration or by aggregation leading to increased presentation to immune cells [28]. The best way to determine this would be to examine the blood from the rats at the final time point for antibodies against AQ.

37. A second point to make from this poster regards figure 7 and the representative western blot. The graph in figure 7 shows a value for the oral dose of 0 mg/kg suggesting to the untrained reviewer that the whole brain homogenate from these rats contained trace amounts of AQ. As an investigator who has performed thousands of immunoblots throughout my career, I can say that is most likely not the case. Antibodies bind to either 1) 8-10 linear amino acids from a protein or 2) a structural 3-dimensional shape that a protein folds into. Most antibodies used for western blots are chosen because they bind to the 8-10 amino acid sequences and not, as stated by Dr.Bazinet, only 4 amino acids. In this respect he is simply wrong. The sequence of 8-

10 amino acids, while present in the protein that the antibody is targeted against, is not necessarily unique to that protein. In fact, it is not at all uncommon to have cross-reacting bands on a western blot. Thus, in contrast to Dr. Bazinet's opinion, it would not be impossible for an antibody to bind to a protein in the whole brain homogenates that had never been exposed to AQ. In fact, there is a high degree of similarity of AQ to several other proteins found in diverse organisms including salad greens, sheep, a common tapeworm and a jellyfish found off the coast of California.

38. To verify a protein on a western blot, the size of the protein is also compared against a standard that is run alongside the samples to determine if the band that is visible is in fact the protein you want to see. Furthermore, the quantification of the protein on the western blot is far from an exact science. The quantification is actually the black mark that is visible on the figure in figure 7. The computer counts any black pixels in that square. That may include: smudges, cross-reacting bands, bad pixels on the camera, faults in the western blot membrane, inappropriate binding of the secondary antibody, inappropriate binding of the enzyme conjugate, or stray light photons in the box. These all may account for the few pixels that are counted on a seemingly negative well. Thus, values above zero for a lane that is expected not to react to the antibody would not be unheard of and in fact would be quite common.

39. A scientist well versed in molecular biology would and should have recognized the common techniques and terminologies used in this poster and would not have difficulty concluding that AQ when delivered orally to rats: 1) accumulated in the hippocampus following a dose of 48 mg/kg, and 2) promoted neuronal survival in an *ex vivo* assay of oxygen/glucose ischemia. Clearly, Dr. Bazinet had significant difficulty understanding the data and techniques displayed in the poster.

Conclusion

40. Based upon the foregoing, it is my opinion that it is not impossible for AQ to pass through the BBB or, for that matter, even if it were impossible for AQ to pass through the BBB, it wouldn't necessarily follow that AQ could not have an effect on brain chemistry.

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November 9, 2015

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Education:

2000	PhD	University of Wisconsin - Madison Medical Microbiology & Immunology
1994	BS	University of Wisconsin - Madison Bacteriology

Research and/or Professional Experience:

2013 – present	Staff Research Associate II, Department of Neuroscience University of California, La Jolla, CA
2012 – present	Associate Editor Journal of Neurodegenerative Diseases
2011 – present	Founder Acridine Consulting, San Diego, CA
2008 – 2013	President/ Chief Scientist NeuroTransit, Inc, San Diego, CA.
2006 – 2011	Project Scientist, Department of Neuroscience UCSD, La Jolla, CA. Field of Study: Therapeutic approaches for the clearance of proteins in neurodegenerative diseases.
2000 – 2006	Post-doctoral Research Associate, Laboratory of Genetics The Salk Institute for Biological Studies, La Jolla, CA Field of Study: Develop gene therapy approaches for the treatment of neurological degeneration of inherited metabolic disorders.
2005	Organized a hands-on scientific experience for over 100 members of the California bar for the 2005 California Science and the Law Conference.
1998 – 2000	Graduate Research Assistant, Department of Ophthalmology University of Wisconsin – Madison Field of Study: Utilize an attenuated HSV-1 virus to deliver the FGF2 cDNA to the retina to treat retinal degeneration.
1998 – 2000	Medical Microbiology & Immunology Graduate Student Representative
1995 – 1998	Teaching Assistant, Department of Medical Microbiology & Immunology and University of Wisconsin Medical School University of Wisconsin – Madison
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Manuscripts and Publications:

1. Valera E, **Spencer B**, Masliah E. Immunotherapeutic Approaches Targeting Amyloid ß, α-Synuclein and Tau for the Treatment of Neurodegenerative Disorders. Immunotherapies. 2015.

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33. Expert Report of Michael A. Pezzone, M.D., Ph.D.
34. Plaintiff Racies' Notice of Motion and Motion for Partial Summary Judgment and all accompanying documents filed therewith
35. Notice of Motion For Summary Judgment of Defendant Quincy Bioscience, LLC and all accompanying documents filed therewith
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EXHIBIT F

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

PHILLIP RACIES, On Behalf of Himself and All Others Similarly Situated,
Plaintiff,
vs.
QUINCY BIOSCIENCE, LLC, a Wisconsin limited liability company,
Defendant.

Case No. 3:15 CV 00292

HIGHLY CONFIDENTIAL

VIDEOTAPED DEPOSITION OF
RICHARD GOODMAN
November 25, 2015
9:08 a.m.
353 North Clark, Suite 1800,
Chicago, Illinois

Reported by:
Deanna Amore, CSR, RPR, 084-003999
PAGES 1 - 292

MR. TANG: Objection. Vague.

But you may answer.

THE WITNESS: First, to clarify, I used a test tube assay that is not necessarily meant to mimic what goes on in the stomach of every individual human being and is not an in vivo study that I conducted. It's an in vitro study.

So I do not know what happens in every stomach of every individual.

If -- and I think there is more information that we'll get to over the next hour or few hours where I've expressed specific opinions about what apoaequorin could be broken down to by pepsin.

BY MR. WELTMAN:

Q. So I'm sorry. Are you done?

A. Yes, I am.

Q. Your opinion is limited to what apoaequorin can be broken down into by pepsin?

A. That, I think, is the question that is being addressed here. We're talking about the digestion of apoaequorin in the stomach by pepsin or in the test tube assay that I conducted, which is only including pepsin.

Q. Okay. I understand that that's what you tested in the Allergenicity Study of 2010, but my

question is a little more specific.

I'm trying to find out what your opinions are going to be about.

A. Okay.

Q. Okay. So I'm asking you, just so I can further understand what your report means and maybe, actually, limit my questioning, quite frankly, and shorten the deposition. So what -- just so you understand, I am trying to find out, are your opinions in your report limited to the digestion of apoaequorin by pepsin?

A. They are because that's what the test was designed for was to do, a pepsin digestion assay for the purpose of evaluating the probability or the -- it's not a real probability number, but the general possibility that this protein would be a likely source of new food allergy. That's what I was asked to do.

Q. So are your opinions in your report limited to opinions regarding the Allergenicity Study of 2010 and how you contend Dr. Bazinet purportedly misunderstood that; is that correct?

A. Okay. So my understanding is that I wrote a subsequent analysis that I think you have a copy of, which is my analysis; is that correct?

apoaequorin, is it, in your assay?

A. In my test tube assay, which does not mimic and is not intended to mimic what goes on in your stomach, it would appear to be digested to fragments of no more than about 3,000 daltons in a fairly rapid fashion.

Q. Okay. And the reason that your assay, the one you used in the 2010 allergenicity study is used is because it is used to predict what is likely to happen in the stomach, correct?

A. No, that's not correct. It is predicted -- it's predictive of whether a protein is more likely or less likely to be a food allergen.

Q. Okay.

A. And if I may qualify that, there are clearly stable proteins that are rock solid stable in the assay that are never shown to be an allergenic in anybody, and there are proteins that are allergens that are digested pretty rapidly in this assay. So it's not a perfect prediction.

Q. Okay. What proteins are deemed to be rock solid in the assay?

A. Concanavalin A --

THE COURT REPORTER: Say that again.

happens after it gets past the stomach?

MR. TANG: Objection. Vague.

THE WITNESS: I am suggesting that I did not -- I provided some references that demonstrate that peptides from dietary proteins can be absorbed through the intestine and actually pass through serum and into mother's milk through the lacrimal glands.

BY MR. WELTMAN:

Q. I will get to that. Let's go to Point No. 2 on paragraph 8 of Dr. Bazinet's report.

He says "A daily dose of Prevagen only provides a trivial amount of amino acids compared to the substantial amount of amino acids supplied by other proteins in our daily diets."

What's wrong with that statement?

A. I think at face value the statement is fine because if you look at the total amino acid content of what is, I understand, a dose of apoaequorin, it is a trivial amount compared to the amount of proteins consumed, but I do not believe that individual amino acids make up the effect of apoaequorin. And so I think it's kind of an irrelevant statement.

Q. What do you mean "make up the effect"?

What effect?

A. If there is -- and I'm not here, as we discussed -- I am not here testifying as to the functionality for memory or whatever is claimed, but if there is an effect of any kind that's specific to apoaequorin, it would have to do with either the whole protein or peptides of the protein in my opinion.

Q. Large peptides or small peptides?

A. Some of the peptides that have functional effects in humans through the diet are as small as di-peptides, but that's very unusual -- meaning two amino acids -- but most of them are probably nine or larger, meaning nine amino acids or larger.

Q. Okay. When you say "functional effects," what do you mean?

A. I mean that they have something that can be measured, whether it's a nervous effect, whether it's an effect on the immediate cell that they're contacting.

Q. And, again, you don't know what percentage of the total amount of protein that's ingested by any of these dietary proteins, what percentage would be one of these, what you call, functional peptides?

barrier, directly affect brain function or memory, do you?

MR. TANG: Objection. Vague.

You may answer.

THE WITNESS: I do not know. I am not a neurobiochemist or neurobiologist. However, there are clearly signaling peptides, proteins made in the body, hormones, that do get in and impact the blood-brain barrier, go through the blood-brain barrier, as far as I know from my general biology training.

BY MR. WELTMAN:

Q. So, again, with regard to paragraph 13 where Dr. Bazinet says "Thus, before apoaequorin even enters the intestine, it has been reduced down to amino acids and possibly some small peptides."

You disagree with that, huh?

A. I'm saying that the evidence to date has not proved that, and the context of how it's ingested and whether the gelatin capsule is important and how the individual's physiological process of digestion occurs on a given event will impact that statement.

Q. And you think it would vary widely -- widely from person to person?

A. Yes.

Q. So then you're saying that the digestion characteristics of apoaequorin were similar to those of common non-allergenic dietary proteins, correct?

A. In terms of the full range or near -- the large size peptides, yes.

Q. Okay.

A. Because we are limited in what we can detect.

Q. But its characteristics are similar to those of common non-allergenic dietary proteins, correct?

MR. TANG: Objection. Mischaracterizing testimony and document.

THE WITNESS: There are many aspects of proteins that have nothing to do with allergenicity. They have to do with functionality. We don't deal with that at all.

So what the statement says, what this study says, what our conclusions are is that apoaequorin would not present an unacceptable risk of food allergy based on a commonly accepted scheme that regulators in the U.S. and Japan and New Zealand, Australia and Europe have agreed is a reasonable

When you wrote this, you believed it was accurate, correct?

A. I still believe it's accurate.

Q. Thank you.

A. But I think it doesn't have anything to do with getting down to peptides.

Q. Okay. Now let's go to your report, Exhibit 2. It's on page 3 of your report, and the header is "The Allergenicity Study of 2010 Does Not Indicate 'Complete' Digestion of Apoaequorin Consumed By Humans."

Now, other than Dr. Moran in his other report and the statement by the law firm -- actually, the statement by Quincy through its law firm, who else has ever said that?

A. I apologize. I lost concentration. Where are we?

Q. Oh, we are on page 3 of your report.

A. Okay.

Q. The header is "The Allergenicity Study of 2010 does not indicate complete digestion of apoaequorin consumed by humans."

A. Okay. Yes.

Q. Who has ever said that?

A. Who has said what?

susceptible to extensive hydrolysis by sequential gastric, pancreatic and small intestinal brush border membrane (BBM) peptidases. The sequences that are taken up at nano-molar or pico-molar concentrations can undergo fast hydrolysis in the blood."

Do you see that?

A. Yes.

Q. Is that generally true for dietary proteins?

A. I don't know if it's generally true to that level. That's a pretty small level that is being quoted, but in general, I think one might assume that. But, clearly, there are exceptions where peptides have functional properties that are not digested.

Q. Okay. And as far as we know, we know of no peptides that are produced by the digestion of apoaequorin that fit what you just described?

MR. TANG: Objection. Vague.

But you can answer.

THE WITNESS: I do not know that the mechanism of action is exactly known.

BY MR. WELTMAN:

Q. Now, it goes on on the left -- on the

BY MR. WELTMAN:

Q. So then the first sentence in paragraph 33 should have said "Dr. Bazinet also appears to have thought that apoaequorin would be completely digested to single amino acids and possibly some small peptides"?

A. That is correct.

Q. Okay. So you want to correct that, right?

And then you say, in the next sentence "There is no evidence of that" -- which again, I don't understand because -- well, how does the second sentence make sense now that you've corrected the first sentence?

Is there no evidence -- strike that?

Your next statement is "There is no evidence of that." Is that because he hasn't performed this yet-to-be described study on apoaequorin?

A. I base that statement on two things:

No. 1, he did not produce a study that would demonstrate that and to my knowledge nobody else has; and No. 2, our study did not measure single amino acids or very small peptides.

The smallest we could possibly detect is in the range of 22 to 30 amino acids, which I do

not call a small, short peptide. To me small, short peptides means like in the range of three to five, six amino acids possibly.

Q. So it's your view that in the stomach, in vivo, apoaequorin would be digested into peptides, correct?

A. Some of it. Maybe most of it would be digested, to some extent that I do not know, have not measured and it could be that there 30-mer, 50-mer, 100-mer. I cannot predict without doing the measurement.

Q. Now, you did this PeptideCutter thing. That's just a software that you can plug something into and do it online?

A. Absolutely.

Q. And it simulates how a protein, in this case, could be digested at pH 1.3?

A. It predicts optimal and maximal degradation based on the sequence and based on the enzymes and the conditions of pH.

Q. Did you carefully look at your PeptideCutter Exhibit C?

A. I did.

Q. Did you see that it indicates, in fact, under your PeptideCutter where only pepsin is used

evidence from the Allergenicity Study of 2010 or anywhere else that apoaequorin is completely digested to single amino acids by pepsin (or any other digestive enzymes for that matter)" -- and I can't read the next word. What is it?

A. "In an in vitro."

Q. "...in an in vitro assay, let alone in the normal physiological conditions in a human body before the protein or peptides generated from the protein, can be absorbed by the body."

When you use the word "or any other digestive enzymes for that matter," does that mean that you're contending that apoaequorin cannot be completely digested into single amino acids as a by-product of the entire digestive process?

A. I wrote this as a scientist, and when I'm saying evidence or no, what I mean is evidence from an experiment, something that can be replicated. I am unaware of any evidence that says apoaequorin would be digested to single amino acids or very small peptides with pepsin alone or with any combination of other proteases that are present in the human body.

Q. And that's because you are unaware of that study that you said would be difficult to perform?

the intestine, huh?

A. I do not.

Q. So your hypothesis is that it's possible that a unique peptide is generated in the stomach and somehow, some unknown amount of this unique peptide doesn't get fully digested in the intestine and ends up somewhere in the body, correct?

A. That is correct.

Q. And this is, of course, speculation, correct?

A. Certainly.

Q. Okay. And then, in addition to that, your hypothesis requires that this particular unique peptide have some pharmacologic or biologic effect that would provide some benefit to the brain?

A. Presumably, I mean I'm not responsible for those studies nor have I read the effects. I did not read the full set of documents.

Q. Well, you give opinions about bioactivity, don't you?

A. I know that there are many bioactive peptides and small proteins that are going through areas, tissues, et cetera, and they can be digested. They can be absorbed. They can trigger through specific intracellular mechanisms.

Q. And then on page 23 of 37, they, again -- under "Summary and Discussion"; do you see that?

A. Yes.

Q. They say "The findings from an in vitro study suggest that apoaequorin dissolved in simulated gastric -- gastric fluid is rapidly digested by pepsin enzyme. In less than 30 seconds, over 90 percent of apoaequorin was digested, and by two minutes almost all of the protein was digested."

They gone on to state, quote, "This suggests that following oral consumption by humans, apoaequorin is likely to be completely hydrolyzed to individual amino acids that will be absorbed in a process similar to other dietary proteins."

Do you believe that that is an accurate statement?

A. I think that's partly speculative.

Q. So you think that there is -- they submitted a false statement to the FDA?

A. I do not --

MR. TANG: Objection. Calls for speculation.

THE WITNESS: Yeah. I do not think they submitted a -- it depends on -- you know, that statement about digestion to amino acids, it

depends, again, on where you are talking about on the digestive tract.

If you look back at what we found in the study is what they reported here, that at two minutes there is still a faint smear peptide that's probably 3.5 kg, which says that it's not immediately digested to individual amino acids.

BY MR. WELTMAN:

Q. Well, I'm just asking, they say that it's going to be absorbed in a process similar to other dietary proteins. Do you have any basis to disagree with what the attorneys in this case said to the FDA on behalf of Quincy?

MR. TANG: Objection. Asked and answered.

THE WITNESS: I don't have a basis to say, no, I don't in terms of proof, physical evidence.

MR. WELTMAN: Could you read back that answer and the question?

(Whereupon, the record was read.)

BY MR. WELTMAN:

Q. Okay. So just to make it clear on the record, you have no basis to contest what Quincy, through its attorneys, said to the FDA, that apoaequorin will be absorbed in a process similar

of the protein would be down to amino acids like very small peptides, but according to my understanding of biology, that is not necessarily true.

BY MR. TANG:

Q. Now, let's turn to your own report, Dr. Goodman, that's Exhibit 2 to this deposition on page 13, paragraph 59 --

MR. WELTMAN: Hold on. You have to let me get there. What paragraph?

MR. TANG: 59.

MR. TANG: Towards the end of the report.

MR. WELTMAN: Sure.

THE WITNESS: Thanks.

BY MR. TANG:

Q. Counsel for plaintiff was asking you about the first sentence earlier, correct?

A. Yes, he read it.

Q. And the first sentence reads "In conclusion, Dr. Bazinet's opinion that apoaequorin must be thoroughly digested to individual amino acids or possibly some very small peptide fragments in the stomach of the consumers is not supported by the robust pepsin digestion assay."

Did I read it correctly?

A. You read it correctly.

Q. While you were drafting your rebuttal report, was this one of the opinions you rebutted?

MR. WELTMAN: Objection. Leading.

MR. TANG: When I drafted the report, except for some very minor formatting changes and a word here or there, the report is my thinking, my thoughts, my interpretation of science, and what I was trying to say in paragraph 59 is that as I read Dr. Bazinet's opinion, he was stating that apoaequorin would be digested to individual amino acids or possibly some very small peptide fragments in the stomach of consumer.

And I wanted to point out with this statement that our pepsin digestion assay did not support that notion, and I did not go too much further. But the reason I was making that conclusion was because we use a stable standard pH 1.2 or 2. We have an overabundance of pepsin relative to stomach conditions in most people, and the stomach clearance is such that you end up with a lot of partially digested or possibly even undigested proteins that go into the intestine.

BY MR. TANG:

Q. All right. So just a couple of things in

When was this submitted to the Court? Are you misstating the record?

BY MR. WELTMAN:

Q. Please answer the question.

A. So the -- I could have been more clear, and I could have said it is almost impossible to assume that you would find single peptides being digested by pepsin, a single amino acid being digested by pepsin, but I did not. I was giving a conservative estimate.

It says, in essence, that even if you got one or two free amino acids produced through the acting of pepsin, which should not happen but could in theory, I suppose, that most of the peptides would be at least ten amino acids long.

BY MR. WELTMAN:

Q. All right. I'm not following you now.

You wrote in this report, which will be submitted to the Court by us, if it is not submitted by defendant, you said the predominant end product would be peptides but that means that in this report that you submitted that we're discussing it wasn't the sole endpoint, correct?

MR. TANG: Asked and answered.

THE WITNESS: It was -- it would not be the

sole end product. You could get intact protein. You could get peptides of 50. You could get peptides of 10. You would get peptides of 2, 3 and maybe you could get a few single amino acids. But I really -- the end product of pepsin digestion even in vivo is not predominantly single amino acids or even di- or tri-peptides.

MR. WELTMAN: No further questions.

MR. TANG: I think we can end this now.

THE VIDEOGRAPHER: That concludes this deposition. We are going off the record. The time is 5:20 p.m.

EXHIBIT G

IN THE UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

PHILLIP RACIES, on Behalf of Himself and All Others Similarly Situation, Plaintiff,

vs.) No. 3:15-CV-00292

QUINCY BIOSCIENCE, LLC, a Wisconsin Limited Liability Company, Defendant.

The Videotaped Deposition of MICHAEL PEZZONE, Ph.D., called by the Plaintiff for examination pursuant to notice and pursuant to the Rules of Civil Procedure for the United States District Courts pertaining to the taking of depositions, taken before Steven Stefanik, a notary public within and for the County of DuPage and State of Illinois, at Suite 110, 1431 Opus Place, Downers Grove, Illinois, on the 4th day of December 2015.

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in terms of original research?

A. A lot of that can be -- is on my CV. It's fairly extensive and diverse.

I was most recently involved with certain pain pathways in the pelvis, looking at how irritable bowel syndrome overlapped with other chronic pelvic pain disorders.

I was also involved with a company Ironwood. It has an oral peptide that is a treatment for constipation, predominant irritable bowel syndrome. I was specifically looking at the pain pathways that this peptide provided.

Q. Okay. So this oral peptide, tell me a little bit more about it. What is it?

A. Its name is linaclotide.

Q. I'm sorry?

A. Linaclotide, L-i-n-a-c-l-o-t-i-d-e. It's a -- I think it's 14-amino-acid peptide that works on a specific guanylate cyclase C receptor in the GI tract that opens chloride channels. And it has -- is a treatment for constipation, but it also, by various pathways that haven't been well defined, desensitizes pain nerves or makes pain nerves less sensitive.

And I had an animal model that allows

eating basically a hot dog.

BY MR. WELTMAN:

Q. Okay. And so, again, what do you understand to be the difference between nutritional function and biologic function?

A. Well, nutrition is just one -- nutrition enables one to have biologic function. It's -- it's necessary for the body, but something that has specific biologic function has some direct effect other than nutrition alone.

Q. Okay. And it's your understanding that he contended and has opined in this case that apoaequorin after digestion has no biological functions?

A. Yes.

Q. As you defined it?

A. Yes.

Q. Okay. And, again, when you mean biological function, you mean some aspect of apoaequorin or another dietary protein has a function other than nutrient value, correct?

A. Correct.

Q. And -- okay. Have you read the reports of defendant's three other experts?

A. I'm not sure. I don't believe so.

Q. And then it lists six panel members. You see that?

A. Yes.

Q. Again, you don't know of any of these people?

A. Hold on. It looks like the same people. No, I don't.

Q. Okay. Now -- bear with me.

Are you aware of a gastric in-vitro assay using pepsin that's used with the digestion assay for a protein?

A. Yes.

Q. What do you -- what do you -- what's your familiarity with it?

MR. TANG: Objection, vague.

But you may answer.

THE WITNESS: Well, it's an in-vitro model that may not reflect underlying normal physiologic processes. And it's used, I guess, commonly in these kinds of drug analyses, but there are a lot of studies to show that they're not indicative of what is involved with normal digestion of proteins and peptides.

BY MR. WELTMAN:

Q. Well, I mean, I understand it's -- it's

in vitro, so it can't be indicative of -- correct?

I mean, it can't be directly indicative, correct?

A. Right.

Q. Just like an animal model can't be directly indicative of what happens in humans, correct?

MR. TANG: Objection, vague.

THE WITNESS: No, I disagree. Animal models have similar physiologic processes.

This is a test tube using a digestive enzyme that only accounts for 15 percent of actual digestion in the stomach and doesn't account for other factors, other binding of things to proteins that may protect it when you do in-vivo studies.

BY MR. WELTMAN:

Q. Okay. So you -- it's your understanding that pepsin is only 15 percent of the digestion in the stomach?

A. Right. Well, it's the only part that occurs in the stomach. It's only 15 percent, and the stomach isn't necessarily for digestion.

Q. Well, just -- that's a lot, but I just wanted to understand --

A. Okay.

Q. -- your contention that pepsin accounts for

You see that?

A. Yes.

Q. Do you understand what the phrase "stability of the protein in pepsin" means?

A. Correct. Yes, I do.

Q. What does that mean?

A. Well, they're saying -- again, speculating that because they saw that it was rapidly degraded in an in-vitro assay, that it would be less likely absorbed and presented to the immune system and thereby would be less likely to be allergenic.

Q. You think this panel of experts were speculating when they wrote this to the FDA?

A. Yes, I do.

Q. Okay. And you think it's pure unfounded speculation, correct?

A. Well, it's based on the assays they had available, still speculation. And even in the way they wrote it, it's still potential speculation. It's still speculation.

Q. Okay. So when they finish and they state here, quote, The results of this study also suggest that the digestion characteristics of apoaequorin are similar to those of common nonallergenic dietary proteins, you would consider that also to